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OFFICE OF
PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

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SUBJECT: **MGK® Repellent 326**: HED Toxicology Chapter for the Reregistration Eligibility Decision Document (RED)
PC Code 047201, Case: 2215

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Attached is the revised Toxicology Chapter for MGK® Repellent 326 to support the Reregistration Eligibility Decision (RED). This document has been revised to address technical correction comments submitted by the registrant.

MGK® Repellent 326

PC Code: 047201

Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision (or Registration Support) Document

Date completed:
April 6, 2002

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1.0 HAZARD CHARACTERIZATION

The toxicology data base is adequate to characterize the toxicity of MGK® Repellent 326. MGK® Repellent 326 has low acute toxicity via the oral (Toxicity Category III), inhalation (Toxicity Category IV), and dermal (Toxicity Category III) routes of exposure. MGK® Repellent 326 is not a skin irritant (Toxicity Category IV) or eye irritant (Toxicity Category III). It is not a dermal sensitizer.

Toxic effects by MGK® Repellent 326 in experimental animals occur at relatively high doses. Body weight loss is characteristic of chronic exposures. In mice, doses of 500 mg/kg/day in the diet for 18 months caused decreased body weight and body weight gains in both sexes and increased liver /gall bladder weights in both sexes and increased liver histiocytosis in males. In rats doses of 250 mg/kg/day in the diet for two years caused decreases in the absolute and relative kidney weights in males and females. In dogs dietary doses of 148 mg/kg/day for a year inhibited body weight gain. Higher doses in dogs caused a decrease in the liver and kidney weights, liver histological changes (centrilobular hypertrophy, bile duct proliferation and portal fibrosis). High doses in the diet of rats (1000 mg/kg/day) and mice (2000 mg/kg/day) produced increases in the incidence of liver and renal cell tumors in males and female rats and increased the incidence of liver adenomas in female mice and alveolar bronchiolar adenomas in males. These findings were the basis for classifying MGK® Repellent 326 as a B2 carcinogen - probable human carcinogen by HED CPRC. It should be noted that the carcinogenic effects were seen at the limit dose (rats) or at twice the limit dose (Mice) for carcinogenicity testing. MGK® Repellent 326 was tested for bacterial reverse mutation, *in vitro* mammalian cell gene mutation in CHO cells and mouse lymphoma cells and for unscheduled DNA synthesis in rat primary hepatocytes and found negative. Dietary administration of MGK® Repellent 326 at doses reaching 1555 mg/kg/day for 28 days did not produce peroxisomal proliferation, did not induce peroxisomal enzymes or induce cytochrome P-450 microsomal enzymes (MRID 43033301. Subchronic dietary exposures resulted in decreased body weighs at 1000-2000 mg/kg/day. MGK® Repellent 326 did not cause toxic effects after subchronic exposures through inhalation to 0.324 mg/L (60 mg/kg/day) or through dermal application of 100 mg/kg/day for 90 days. Developmental toxicity occurred at high doses (>1000 mg/kg day in rats; >100 mg/kg/day in rabbits) which were higher than those causing maternal toxicity in rats or rabbits. There were also no indications of teratogenic effects in experimental animals. However there is *quantitative and qualitative* evidence of increased susceptibility of the offspring during *in utero* exposure to MGK® Repellent 326 in a two generation reproduction study in rats. Increased susceptibility is evidenced by decreased body weight of pups was noted at 250 mg/kg/day doses compared to the same effect in the parents occurring at 1000 mg/kg/day. Pup mortality was also noted at the 1000 mg/kg/day dose with no parental mortality occurring at this dose.

2.0 REQUIREMENTS

The requirements (CFR 158.690) for MGK® Repellent 326 are in the following table. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1. Data Requirements for MGK® Repellent 326

Test	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (Rodent)	yes	yes
870.3150 Oral Subchronic (Non-Rodent)	yes	yes*
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	yes	yes
870.3465 28-Day Inhalation	yes	yes
870.3700a Developmental Toxicity (Rodent)	yes	yes
870.3700b Developmental Toxicity(Non-rodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (Rodent)	yes	yes
870.4100b Chronic Toxicity (Non-rodent)	yes	yes
870.4200a Oncogenicity (Rat)	yes	yes
870.4200b Oncogenicity (Mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotox. (Hen)	no	-
870.6100b 90-Day Neurotoxicity Hen)	no	-
870.6200a Acute Neurotoxicity. Screening Battery (Rat)	no	-
870.6200b 90 Day Neurotoxicity Screening Battery (Rat)	no	-
870.6300 Develop. Neurotoxicity	no	-
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	yes	yes
Special Studies for Ocular Effects	no	-
Acute Oral (Rat)	no	-
Subchronic Oral (Rat)	no	-
Six-month Oral (Dog)		

* The requirement of a subchronic study is satisfied by the chronic study in dogs.

3.0 DATA GAP(S)

The toxicological data base for MGK® Repellent 326 is adequate for hazard characterization.

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of data base for acute toxicity: The data base for MGK® Repellent 326 acute toxicity is considered complete (Table 2). No additional studies are required at this time.

Table 2: Acute Toxicity Data on MGK® Repellent 326

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
870.1100	Acute Oral	00155068	LD_{50} = 5850 mg/kg, % 4270 mg/kg & 5120 mg/kg % + &	III based on female toxicity
870.1200	Acute Dermal	41648601	LD_{50} = > 2000 mg/kg	III
870.1300	Acute Inhalation	41571501	LC_{50} = > 6.09 mg/L	IV
870.2400	Primary Eye Irritation	41800501	not an eye irritant	III
870.2500	Primary Skin Irritation*	41826505	not a skin irritant	IV
870.2600	Dermal Sensitization	41648602	not a skin sensitizer	NA

* liquid in aerosol material tested.

MGK® Repellent 326 has low to moderate toxicity in experimental animals by the oral (Category III), dermal (Category III) and inhalation routes (Category IV). It is not any eye (Category III) or skin irritant (Category IV). It is not a skin sensitizer either.

4.2 Subchronic Toxicity

Adequacy of data base for subchronic toxicity: The data base for subchronic toxicity is considered complete.

870.3100: 90-Day Oral Toxicity - Rat

In a subchronic range-finding study (MRID 42093901), MGK® Repellent 326 (Lot # 3716;

purity 100% provided in MRID 42400101, HED # 009831) was administered to groups (10/sex/dose) of CD-1 rats (6 weeks old weighing 183-216 g for males and 137-162 for females) at nominal concentrations of 0, 125, 250, 500, 1,000 or 2,000 mg/kg-body weight/day (2X limit dose) in the diet for 13 weeks.

There were 11 deaths reported (one male and one female in the 125 mg/kg/day group; one female each from the 500 and 1,000 mg/kg/day groups and seven females from the 2,000 mg/kg/day group). The deaths in the 1000 mg/kg/day groups and lower were not treatment related and did not exhibit clinical signs. Two of the rats that died in the 2000 mg/kg/day group had tremors and abnormal gait in one rat and loss of righting reflex in the other rat. Observations that were noted only in the 2000 mg/kg/day group included decreased defecation, labored breathing and hunched posture. No treatment-related clinical effects were observed in the 125, 250, 500, or 1000 mg/kg/day animals. Ophthalmoscopic examinations, urinalysis, and microscopic pathology were not performed.

Statistically significant decreases in body weights relative to concurrent controls occurred in the 2000 mg/kg/day group (46.6% decrease in males and 29.2% decrease in females, $p<0.01$) and in the 1000 mg/kg/day group (12.6% decrease in males and 11.1% decrease in females). The decreases in body weight corresponded to decreased food consumption in these two groups. Erythrocyte counts, hemoglobin, hematocrit, and reticulocyte counts were significantly increased ($p<0.01$) from the controls and platelets were significantly decreased from the controls ($p<0.01$) in the 2000 mg/kg/day males and females. In the 1000 mg/kg/day group, the erythrocyte, hemoglobin, hematocrit and reticulocytes values of the males were significantly decreased ($p<0.5$-0.01). These hematological changes do not appear to be treatment related. Other effects of MGK 326 feeding were significant increase in some biochemical parameters. Aspartate aminotransferase and alanine transferase were significantly increased in the male 2000 mg/kg group and alkaline phosphatase was increased in the females ($p<0.01$). Similarly, upward trends were noted in the total bilirubin, cholesterol and urea nitrogen values. A definite treatment-related decrease in the male absolute spleen weights in the 2000 mg/kg ($p<0.01$) and the 1000 mg/kg group ($p<0.05$) was noted. Other treatment-related changes were significant decreases in absolute kidney, liver, heart and testis weights of the 2000 mg/kg males. A significant decrease in the absolute weight of the right kidney ($p<0.01$) and right testis ($p<0.05$) was also noted in the 1000 mg/kg group when compared to controls. Macrosopic findings related to treatment were noted in the 2000 mg/kg group. In this group the livers in both males and females were mottled with tan, multilobar foci, enlarged or congested. The stomachs (glandular/non-glandular) had erosion of the mucosa (males and females) and hemorrhage of the submucosa (females).

Based on the reduction in body weights in both sexes, and organ weight decreases in males of the 1000 mg/kg/day group the systemic **LOAEL** is 1000 mg/kg/day and the **NOAEL** is 500 mg/kg/day.

In conjunction with the carcinogenicity study in rat (MRID 42093902), the submitted study is

classified as **acceptable/guideline** (OPPTS 870.3100 [§82-1a]; OECD 408) and satisfies the requirements for a subchronic oral toxicity study in the rat.

870.3100: 90-Day Oral Toxicity - Mouse

In a 90-day oral toxicity study (MRID 42100101), MGK Repellent 326 (Lot #: 3716; 100% purity was reported for this lot in MRID 42400101) was administered to 10 CD-1 mice/sex/dose in the diet at nominal dose levels of 0, 125, 250, 500, 1000, or 2000 mg/kg/day (2x limit dose).

No unusual clinical observations were attributed to treatment. Mortality was unaffected by treatment. Food efficiency was not reported. Ophthalmoscopic examinations, blood analyses, urinalysis, and microscopic pathology were not performed.

In the 2000 mg/kg/day males, increased food consumption (819-54%; $p<0.05$) was observed during Weeks 3-13. Despite the increased food consumption, body weights were decreased ($p<0.05$) relative to the concurrent controls (912-17%) throughout the study. The terminal body weight was also decreased (914%; $p<0.01$). A decrease in cumulative body weight gains was observed at Weeks 0-4 (971%) and 0-13 (950%).

Liver weights (relative to body) were increased ($p<0.05$) at 2000 mg/kg/day in males (813%) and females (89%) and in the 1000 mg/kg/day males (88%). Right and/or left kidney weights (absolute, relative to body, and/or relative to brain) were decreased ($p<0.05$) at $500 mg/kg/day (97-22%) in males. An ambiguous effect was observed on the kidneys of the females. Relative (to body) kidney weights decreased ($p<0.05$) in the left kidney at 1000 and 2000 mg/kg/day (915-21%), but increased in the right kidney at 500 and 2000 mg/kg/day (815-16%). The weight effects on the kidney do not appear to be treatment related. These effects were seen in a chronic study (MRID 42100102) but were considered related to body weight changes and no evidence of nephrotoxicity was observed. Further support for a treatment-related effect in the liver and kidney in the 2000 mg/kg/day males included a mild white focus (unilateral) in the kidney and a mild tan foci (multilobular) in the liver (1/10 treated mice, each lesion).

The LOAEL is 2000 mg/kg/day based on decreased body weights and body weight gains and increased food consumption and liver (mild tan foci-multilobular) and kidney (mild white focus-unilateral) effects observed in males. **The NOAEL for this study is 1000 mg/kg/day**.

In conjunction with the carcinogenicity study in mice (MRID 42100102), the submitted study is classified as **acceptable/guideline** (870.3100) and satisfies the requirements for a subchronic oral toxicity study in mice.

870.3150: 90-Day Oral Toxicity - Dog

This requirement was satisfied by the chronic study in dogs discussed later.

870.3200: 21/28-Day Dermal Toxicity – Rabbit

This requirement was satisfied by the 90-day dermal toxicity study in rabbbits discussed later.

870.3250: 90-Day Dermal Toxicity – Rabbit

In a 90-day dermal toxicity study (MRID 42427202.), groups of 11-18 weeks old New Zealand white rabbits (10/sex/dose) weighing 2.1-3.4 kg for the males and 2.3-3.2 for the females, were exposed dermally to MGK® Repellent 326 (Lot #3716; 100% purity as provided in MRID 42400101, HED # 009831) at 0, 10, 30 or 100 mg/kg body weight /day (dissolved in corn oil at 1.0 ml/kg body weight) for 90 days at 6 hours/day, 7 days/week. The doses were selected on the basis of a 14-day range finding study (MRID 42427201) in rabbits (2/dose) at 0, 30, 100 or 300 mg/kg/day where moderate to severe skin reactions occurred at 100 mg/kg/day and above. In another 7-day dermal study (not submitted) severe erythema/eschar reactions occurred at the limit dose of 1000 mg/kg/day. The test rabbits were examined twice daily for mortality and once daily for clinical signs. Body weights were determined pretest and weekly during the study. Food consumption was recorded weekly during the study. Eyes were examined at pretest period and prior to terminal sacrifice. All animals received postmortem examination. Various hematological and clinical chemistry parameters were determined on all surviving animals from blood taken at time of terminal sacrifice.

No compound-related clinical signs of toxicity or mortalities were reported. The test material did not have significant effects on body weights or food consumption. No compound related ocular toxicity, clinical chemistry or hematological changes were seen in any dose group. Sporadic changes in these parameters were reported but were not treatment-related. No compound related effects were seen in macroscopic examination of the test animals and the various organ weights were comparable to the control group. The gross histopathology findings were unremarkable for all organs evaluated in the test animals. Minimal changes were noted at the application sites in both control and treatment groups. There were instances of treatment related effects limited to wrinkling and fissuring of the skin. Fissuring of the skin was seen in 5/20 of the high dose rabbits only. Two females in the high dose group had raised red scabbed areas at the test site. Minimal inflammatory and degenerative changes were seen in the brain, kidneys and liver of some control and treatment animals as associated with the presence of the common protozoan parasite *Encephalitozoon cuniculi*.

Based on the dermal effects at the site of application (fissuring and moderate skin reactions) the **LOAEL** for dermal effects is **100 mg/kg/day** and the **NOAEL** is **30 mg/kg/day**. The **LOAEL** for systemic toxicity is **greater then 100 mg/kg/day** since no systemic toxicity was reported at this highest dose tested and the **NOAEL** is 100 mg/kg/day.

This 90-day dermal toxicity study in the rabbit is classified **acceptable/guideline**, and it satisfies the guideline requirement (OPPTS 870.3250 (rodent) [§82-3]; OECD 411).

870.3465: 90-Day Inhalation Toxicity – Rat

In a subchronic inhalation toxicity study (MRID 42990201), groups of 7-week old Sprague Dawley rats (15/sex/dose) weighing 252 gm for the males and 202 gm for the females, were exposed (whole body) to MGK® Repellent 326 (Lot #3716; 100% purity as provided in MRID 42400101, HED # 009831) by inhalation at the analytical concentrations of 0, 0.0105, 0.028, 0.095, or 0.324 mg/L for 6 hours/day, 5 days/week and for a total of at least 67 exposures. The test animals were housed individually and exposed to the aerosols test material in a 1000 L chamber. Samples were withdrawn from the sampling ports for gravimetric analysis. Samples were also withdrawn from 3 different locations in the chamber to determine the test article distribution within the exposure chamber. Samples were also taken for mass median aerodynamic diameter (MMAD) determinations. The analytical results showed good agreement between targeted, mean gravimetric and analytical concentrations. The means for the average MMAD and the average percentage of particles of #1.0 ：m in diameter were 1.4 ：m and 29%, respectively. The test rats were examined twice daily for mortality and clinical signs. Body weights were determined pretest and weekly during the study. Eyes were examined at the pretest period and prior to terminal sacrifice. All animals received postmortem examination. Various hematological and clinical chemistry parameters were determined for all surviving animals from blood taken at terminal sacrifice time. The lungs of all test animals were examined histologically. Other tissues were examined histologically only from the control and high dose groups.

No compound-related clinical signs of toxicity or mortalities were reported. Two deaths unrelated to the treatment were reported. The test material did not have significant effects on body weights or food consumption. No compound related ocular toxicity or hematological changes were seen in any dosed group. Statistically significant increases in the levels of alkaline phosphatase in males and glucose in females were noted with no apparent dose-related response. No compound related effects were seen in macroscopic examination of the test animals and the various organ weights were comparable to the control group. An increase in the incidence of histological changes were mostly seen in the respiratory tract of test animals. These findings included epithelium-intracytoplasmic eosinophilic material in nasoturbinates and hyperplasia of the mucosa of the nasolarynx, particularly in the high dose animals.

Under conditions of this study, MGK® Repellent 326 did not produce any compound-related systemic toxicity. The histopathological changes in the nasoturbinates and the nasolarynx, in the high dose animals were considered to be adaptive responses. The **LOAEL** for MGK® Repellent 326 in this test is **>0.324 mg/L** (60 mg/kg/day calculated based on inhalation rate of 223 L/day and rat weight of 300 g) and the **NOAEL** is **0.324 mg/L (60 mg/kg/day)**. This subchronic 90-day inhalation toxicity study in the rat is classified **acceptable/guideline**, and it satisfies the guideline requirement (OPPTS 870.3465 [§82-4]; OECD 413).

4.3 Prenatal Developmental Toxicity

Adequacy of data base for Prenatal Developmental Toxicity: The data base for prenatal developmental toxicity is considered complete. No additional studies are required at this time. There was no evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure. The effects observed in these species occurred at maternally toxic doses.

870.3700a: Prenatal Developmental Toxicity Study - Rat

In a prenatal developmental study (MRID 41987802), MGK® Repellent 326 (Lot # 3716; 98.8% purity) was administered to groups (24/group) of Sprague-Dawley Crl:CD BR mated and presumed pregnant rats (10.5-12 weeks age and weighing 210-286 gm at mating) by oral gavage in 1.0% carboxymethylcellulose suspension at dose levels of 0, 100, 300 or 1000 mg/kg/day from days 6 through 15 of gestation. These doses were selected on the basis of a range finding study (MRID 41987801) where groups of presumed pregnant Sprague-Dawley Crl:CD BR rats were dosed once daily by gavage with MGK® Repellent 326 at dose levels of 0, 100, 200, 400 or 800 mg/kg/day from days 6 through 20 of gestation and no maternal or developmental effects were noted at these dose levels. Therefore the limit dose of 1000 mg/kg/day was selected for the high dose in the main study. The dams were sacrificed on Day 20 of gestation by CO_2 asphyxiation and fetuses removed by cesarean sectioning.

No treatment-related mortality, clinical signs or gross pathological observations were noted. The mean gravid uterine weights of the treated groups were slightly lower than the controls suggesting a dose response, but the differences were not statistically significant. The mean gravid uterus weights were 90.6 ± 14, 88.4 ± 19, 86.5 ± 22, 84.5 ± 18 g in the control, low-, mid- and high-dose groups, respectively. A statistically significant decrease in body weight gain (14.5% decrease compared to the control; $p<0.01$) over the 6-15 days of the gestation period was recorded for the 1000 mg/kg/day dose group. Cesarean section observations (abortions, total number of litters, total corpora lutea and corpora lutea/dam, implantations, live fetuses, resorptions, pre- and post-implantation loss and fetal body weight) were comparable to the control group. There were no treatment-related effects on the developing fetuses. No major external/visceral abnormalities were noted in any of the test groups. The **LOAEL** for maternal toxicity of MGK® Repellent 326 in the rat is 1000 mg/kg/day based on reduced body weight gain at this level and the **NOAEL** for maternal toxicity is 300 mg/kg/day. Since no developmental toxicity was observed at the limit dose of 1000 mg/kg/day, the **LOAEL** for this effect is >1000 mg/kg/day and the developmental toxicity **NOAEL** is 1000 mg/kg/day.

This developmental toxicity study in the rat is considered **acceptable/guideline** and it satisfies the guideline requirement for a developmental study in the rat (OPPTS 870.3700b [§83-3a]; OECD 414) .

870.3700b: Prenatal Developmental Toxicity Study - Rabbit

In a developmental toxicity study (MRID 40433301), MGK® Repellent 326 (Lot/batch # 3716;

100% purity, provided in MRID 42400101) was administered in 0.5% methylcellulose orally via gavage, in a dosing volume of 3 mL/kg, to16 female New Zealand White SPF rabbits/group, at dose levels of 0, 35, 100, or 350 mg/kg/day, on gestation days (GD) 7 through 19. All surviving does were sacrificed on GD 29 and their fetuses were removed by cesarean section and examined.

When compared to concurrent controls, no treatment-related changes were observed in the number of corpora lutea, number of implantations, number of live and dead fetuses, number of resorptions, fetal weights, sex ratios, or post-implantation losses at 35 or 100 mg/kg. These parameters could not be evaluated at 350 mg/kg due to high mortality. No treatment-related gross pathological findings were noted at any dose tested. Food consumption was not measured during the study.

In the 350 mg/kg/day group, nine does died (GD 9-19) and five does were sacrificed *in extremis* prior to scheduled cesarean section. Clinical signs prior to death included leaning to the left, labored breathing, involuntary eye movement, dry white material in nasal area, decreased motor activity, and no righting reflex. It should be noted that the incidences of these clinical signs were low and were not noted consistently among all animals that died prematurely; several animals that died or were sacrificed *in extremis* displayed no clinical signs of toxicity. These deaths were considered to be treatment-related. Decreased ($p<0.01$) body weight gains were observed during GDs 7-9 (-177 g treated vs. 29 g controls) and GDs 9-12 (-95 g treated vs. 25 g controls). During the second half of gestation and the overall treatment interval, high mortality precluded assessment of body weight gains. In addition, adjusted (for gravid uterine weight) body weights could not be evaluated at this dose.

The maternal LOAEL is 350 mg/kg/day based on mortality preceded by decreased body weight gains. The maternal NOAEL is 100 mg/kg/day.

Due to high mortality in the 350 mg/kg/day does, fetal toxicity at this dose could not be evaluated. No fetal toxicity was observed at 35 or 100 mg/kg/day.

The developmental toxicity LOAEL was not observed. The developmental toxicity NOAEL is 100 mg/kg/day.

Based on the dose rationale for the range finding study, no toxic effects were observed in the does at 250 mg/kg/day. Therefore, it would have been preferable if the Sponsor had chosen additional doses between 250 and 350 mg/kg/day for the definitive study in order to demonstrate the sublethal effects of MGK Repellent 326.

This study is classified **acceptable/guideline** (OPPT 870.3700b; OECD 414) and satisfies the requirements for a developmental study in the rabbit.

4.4 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity is considered complete. No additional studies are required at this time. There is *quantitative and qualitative* evidence of increased susceptibility of the offspring during *in utero* exposure to MGK® Repellent 326 in a two generation reproduction study in rats. Quantitative susceptibility was based on offspring toxicity occurring at a lower dose (250 mg/kg/day based on decreased pup body weight) than that causing parental toxicity (limit dose of 1000 mg/kg/day causing decreased body weight mainly). Qualitative susceptibility was based on the occurrence of pup deaths but no parental deaths at 1000 mg/kg/day.

870.3800: Reproduction and Fertility Effects - Rat

In a 2-generation reproduction toxicity study (MRID 41547801), MGK® Repellent 326 (Lot/batch #3716; 100% purity) was administered continuously in the diet to COBS® CD® rats (26/sex/dose) at nominal dose levels of 0, 65, 250, or 1000 (limit dose) mg/kg/day throughout premating, gestation and lactation.

When compared to concurrent controls, no treatment-related changes were observed in the following parameters: mortality, clinical signs, reproductive performance, and gross pathological findings in the F_0 or F_1 adults; mean litter size, viability indices, sex ratios, or gross pathological findings in the F_1 or F_2 pups. Reproductive function was not evaluated in the F_0 or F_1 adults. Anogenital distance, offspring developmental landmarks, organ weights, and histopathology were not evaluated in the F_1 or F_2 pups.

At 1000 mg/kg, decreases in **body weights** occurred throughout premating in the P adults ($p<0.05$ or 0.01) when compared to both control groups. Reductions ($p<0.05$ or 0.01) were also observed in the F_0 females throughout gestation and lactation for the F_{1a} and F_{1b} matings. In the F_1 animals, decreased ($p<0.05$ or 0.01) body weights were observed during the premating interval in the males and females and during gestation and lactation for the F_{2a} and F_{2b} matings. When compared to the mean of both control groups, body weight gains were reduced in the F_0 males and females during the premating interval. During gestation and lactation, body weight gains were decreased relative to the mean of both control groups, but were not statistically different from either control group at any interval. Overall body weight gains were decreased during GDs 0-20 and LDs 0-21 for the F_{1a} and F_{1b} matings; however, the standard deviations associated with the body weight gains were large, and therefore, the decreases were equivocal. In the F_1 generation, decreased body weight gains relative to the mean body weight gains of both control groups were observed in the males throughout the premating interval and in the females during weeks 4-17 only. Overall body weight gains were decreased during GDs 0-20 and LDs 0-21 for the F_{2a} and F_{2b} matings; however, the standard deviations associated with the body weight gains were large, and therefore, the decreases were equivocal.

In the F_0 animals, absolute **food consumption** (g/animal/day) was decreased ($p<0.05$ or 0.01) in the males and females throughout premating. In addition, food consumption was decreased during gestation for the F_{1a} and F_{1b} matings ($p<0.05$ or 0.01). In the F_1 animals, food consumption was decreased ($p<0.05$ or 0.01) in the males and females throughout premating. In addition, food consumption was decreased throughout gestation for the F_{2a} and F_{2b} matings ($p<0.05$ or 0.01), except for days 7-15 for the F_{2a} mating.

During **histopathological evaluation**, trace to mild biliary stasis and portal bile duct proliferation were noted in the livers of the F_0 high dose females. In the F_1 high dose males and females, trace to mild portal bile duct proliferation and trace portal mononuclear cell infiltrate of the liver were observed. In addition, trace to mild bile stasis was observed in the high-dose females. No treatment-related histopathological changes were observed in the F_0 males.

No treatment-related changes were observed in the low- or mid-dose males and females.

The LOAEL for parental toxicity is 1000 mg/kg/day (limit dose) based on decreased body weights, body weight gains, and food consumption and histopathological liver changes in the males and females. The NOAEL is 250 mg/kg/day.

At 250 mg/kg, **body weights** were decreased in all F_1 pups on PND 21 (p#0.05 or 0.01). In addition, body weights were decreased (p#0.05 or 0.01) in the mid-dose F_{2b} pups at PND 21.

At 1000 mg/kg, increased numbers of F_1 **pup deaths** relative to controls during PND 0-4 (pre-cull) and PND 4 (post-cull) through 21 were noted. In addition, increased numbers of deaths were noted in the F_2 pups during PND 4 (post-cull) through 21. The most commonly noted clinical sign in the F_1 and F_2 pups was small size. This observation corresponds to decreased body weights noted in these animals. **Body weights** were decreased (p#0.05 or 0.01) during PND 1-21 in the F_{1a} and F_{1b} male pups and in the F_{1a} female pups. In the F_{1b} females, body weights were decreased (p#0.05 or 0.01) during PND 4 (post-cull) through 21. In the F_2 males and females, body weights were decreased (p#0.05 or 0.01) during PND 1-21. Overall (PND1-21) body weight gains (calculated by reviewers) were decreased in the F_1 and F_2 pups.

No treatment-related changes were observed in the low-dose pups.

The LOAEL for offspring toxicity is 250 mg/kg/day based on an decreased pup body weights. The NOAEL is 65 mg/kg/day.

The LOAEL for reproductive performance could not be determined because adequate data were not provided.

The reproductive study in the rat is **acceptable/guideline** (pre-1998 guidelines) and satisfies the requirements for a multigeneration reproduction toxicity study in rats **(870.3800; §83-4)**.

However, based on the 1998 FIFRA guidelines, the study had the following deficiencies. Offspring developmental landmarks were not determined. Estrous cycle length and pattern was not determined (F_0 and F_1 females). Sperm concentration, motility, and morphology were not evaluated (F_0 and F1 males). Organs (uterus, testes [for all males], epididymides, seminal vesicles, prostate, brain, pituitary, liver, kidneys, adrenal glands, spleen) from the F_0 and F_1 adults were not weighed. Organs (brain, spleen, thymus) from the offspring were not weighed.

4.5 Chronic Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete. No additional studies are required at this time. The chronic toxicity of MGK® Repellent 326 was investigated in rats, mice and dogs. There was no specific primary target organ of toxicity defined. Decreased body weight gain is characteristic of chronic exposures to MGK® Repellent 326. In mice, doses of 500 mg/kg/day in the diet for 18 months caused decreased body weight and body weight gains in both sexes and increased liver /gall bladder weights in both sexes and increased liver histiocytosis in males. In rats doses of 250 mg/kg/day in the diet for two years caused decreases in the absolute and relative kidney weights in males and females. In dogs dietary doses of 148 mg/kg/day for a year inhibited body weight gain. Higher doses in dogs caused a decrease in the liver and kidney weights, liver histological changes (centrilobular hypertrophy, bile duct proliferation and portal fibrosis). High doses in the diet of rats (1000 mg/kg/day) and mice (2000 mg/kg/day) produced increases in the incidence of liver and renal cell tumors in males and female rats and increased the incidence of liver adenomas in female mice and alveolar bronchiolar adenomas in males. These findings were the basis for classifying MGK® Repellent 326 as a B2 carcinogen - probable human carcinogen by HED CPRC. It should be noted that the carcinogenic effects were seen at the limit dose (rats) or at twice the limit dose (Mice) for carcinogenicity testing.

870.4100a: Chronic Toxicity – Rat

This is discussed in the carcinogenicity study section.

870.4100b: Chronic Toxicity - Dog

In a one year chronic study (MRID 42320602), MGK® Repellent 326 (Lot # 3716; 99.5% purity) was administered to groups (4/sex/dose) of beagle dogs (9 months old weighing 8.2-12.7 kg for males and 7.0-11.1 kg for females) at dietary concentrations of 0, 250, 1,000 or 4,000 ppm (0, 8.27, 34.3, or 148.0 mg/kg/day for males; 0, 8.12, 34.1 or 117.5 mg/kg/day for females) for 52 weeks. These doses were selected on the basis of a 2-month range finding study where beagle dogs (2/sex/dose) received initially in their diet 0, 4,000, 7,500, 15,000/10,000; 30,000/1,000 or 60,000/2,000 ppm of MGK® Repellent 326 (Lot # 3716; 99.5% purity). Due to marked decrease in food intake at the high dose levels, these were reduced to from 15,000 ppm to 10,000 ppm after 15 days, and from 30,000 and 60,000 ppm to 1000 and 2000 ppm,

respectively after 8 days. Treatment-related effects in this range finding study were marked decrease in body weights and food consumption (at doses of 7,500 ppm and above), marked increase in alanine transferase activity in both sexes (15,000/10,000 ppm dogs), a decrease in the liver and kidney weights (7,500 and 15,000/10,000 ppm dogs), a slight decrease in the testicular weights of 15,000/10,000 ppm males and in the ovarian weights of similar group females, liver histological changes (centrilobular hypertrophy, bile duct proliferation and portal fibrosis in the 7,500 and 15,000/10,000 ppm dogs). Therefore, the 4,000 ppm dose was selected as the highest dose in the main study.

The test dogs in the one year study were monitored twice daily for signs of toxicity and mortality. Body weights and food consumption were determined pretest and weekly during the study. Opthalmoscopic examinations were conducted on all dogs pretest and at 12, 25 and 51 weeks of the study. Clinical pathology was conducted on each dog prior to initiation of the study and at 6, 12, 25 and 50 weeks of the study. These included the various required hematological, clinical chemistry and urinalysis parameters. At the study termination gross and histopathological examination were conducted on all the dogs.

All dogs survived the treatment and clinical observations were comparable between the treated and control dogs except one dog from each sex at the 4,000 ppm group showed signs of inappetence and were thin. There was a consistent decrease (statistically not significant) in body weight (15% compared to control dogs) at the 4,000 ppm dose starting from week 2 to the end of the study. Male dogs in this group did not gain any weight by the study end. Female body weights were not affected by the treatment. Food consumption was increased in male and female treated dogs relative to the controls (10-15%) except for a slight decrease (4.2%) in the 4, 000 ppm female dogs. Opthalmological observations, changes in some hematological and clinical chemistry values were noted but were not dose- or treatment-related. There were no changes in the urinalysis parameters and there were no gross pathological treatment-related effects. Organ weight data showed increases in some organ/body weight ratios but were not considered to be compound- or dose-related. There were no histological changes except for an increase in the incidence of congestion of the spleen in the 1,000 (3/4) and 4,000 ppm (3/4) females compared to the controls (1/4). This was not accompanied by any change in the hematological parameters and was therefore considered not to be related to the treatment.

In conclusion, MGK® Repellent 326 did not produce any obvious toxicity after one year of dietary feeding to dogs except depression of body weight of males at the 4,000 ppm. This effect was also noted in a two year rat chronic/carcinogenicity study (MRID 42093902) and a mouse carcinogenicity study (42100102). In addition, in the dog dose range finding study discussed above, there were marked decreases in body weights and food consumption and histopathological changes in the liver. Based on these results, the **LOAEL** for the dogs in this study is 4,000 ppm (148.0 mg/kg/day) based on the inhibition of body weight gain and the **NOAEL** is 1,000 ppm (34.3) mg/kg/day. This one year dietary toxicity study in dogs is considered **acceptable/guideline** and it satisfies the guideline requirement for a chronic non-

rodent toxicity study (OPPTS 870.4100b [§83-1b]; OECD 452).

4.6 Carcinogenicity

Adequacy of data base for Carcinogenicity: The data base for carcinogenicity is considered complete. No additional studies are required at this time.

The HED Carcinogenicity Peer Review Committee (CPRC) classified MGK® Repellent 326 as Group B2 - probable human carcinogen with inadequate evidence in humans (HED memo July 21, 1993). This decision was based on the finding of multiple malignant and benign tumors in the rat and in the mouse. The registrant rebutted this classification and requested a second peer review of the carcinogenicity data based on a re-read of the histological slides by a consultant pathologist. However, for the reconsideration of the previous CPRC cancer classification, the revised pathology diagnosis should be the consensus of a pathology peer review group similar to that employed by the NTP according to Pesticide Regulation (PR) Notice 94-5 dated August 24, 1994. There is no record that such a pathology peer review group had been convened. A Q_1^* based on liver adenomas, carcinomas and combined adenomas/carcinomas in rats was derived (using 3/4's scaling factor) to be 1.63×10^{-3} $(mg/kg/day)^{-1}$ in human equivalents for the male rat and 8.4×10^{-4} $(mg/kg/day)^{-1}$ in human equivalents for the female rat (HED TXR No. 0051402).

870.4200a: Carcinogenicity Study - Rat

In a combined chronic / carcinogenicity study (MRID 42093902), MGK® Repellent 326 (Lot # 3716; purity 100% provided in MRID 42400101, HED # 009831) was administered to groups (60/sex/dose) of CD® rats (6 weeks old weighing 189-217 g for males and 131-151 g for females) at nominal concentrations of 0 (two control groups A & B used), 65, 250, or 1,000 mg/kg-body weight/day (limit dose) in the diet for 2 years. The doses were selected on the basis of a 13-week range finding study with MGK® Repellent 326 (MRID 42093901) at 0, 125, 250, 500, 1000 or 2000 mg/kg/day where treatment -related effects occurred at 1000 mg/kg/day (decreased body weight gain in males, reduced organ weights) and 2000 mg/kg/day (decreased body weight, mortality, labored breathing, hunched posture, decreased defecation, significant alterations in hematological and biochemical parameters and reduced organ weights) levels.

The test compound did not increase mortality or produce clinical signs or ophthalmoscopic abnormalities, or changes in hematological parameters in any treatment group. A treatment-related statistically significant increase ($p<0.05$-0.01) in the alanine and aspartate aminotransferase levels in the high dose males at various examination periods was noted. The alkaline phosphatase level was also increased ($p<0.05$) in the high dose males at the 24 month examination period. For female rats, the clinical chemistry parameters were similar between the treated and the control groups A & B. A decrease in the pH value was seen in the 1000 mg/kg male and female rats (pH of 6) relative to those of the controls A & B (pH of 7) at various examination periods. Body weights were significantly decreased ($p<0.01$) in high dose males

(23% decrease compared to controls A & B) and females (40% decrease compared to both controlgroups). There was also a 16% reduction in food consumption in males and 24% in females relative to both control groups in the high dose males and females. Food efficiency in high dose males and females was reduced and it was statistically significant ($p<0.05$) at several measurement intervals. A decrease in both absolute and relative (to brain) , liver, heart and kidney weights were seen in both high dose males and females. In addition a significant decrease ($p<0.05$) compared to control groups in absolute and relative (to brain) kidney weights were also seen in the mid-dose group males and females.

In the high dose group, the test compound produced increases (well above the historical control incidence) in the incidence of hepatocelluar adenomas (16.6% vs 2.5% in combined control males; 13.3% vs 0.8% in combined control females) and carcinomas (16.6% vs 0% control males; 15% vs 0% control females), hyperplastic nodules (6.6% vs 1.7% in combined control males; 11.7% vs 2.5% in combined control females), and foci of hepatocellular alteration of clear cell type (61.7% vs. 17.5% in combined control males; 76.7% vs 11.7% in combined control females). There was also an increase in the incidence of renal cell carcinomas (well above the historical control incidence) in both males (6.7% vs 0%) and females (5% vs 0%) at this dose level. An increase (within the historical control of the laboratory) in the incidence of benign intersitial cell tumors in the testis and in the incidence of benign uterine tumors (polyps) was seen in the 1000 mg/kg males and females, respectively. A re-read of the kidney slides by IRDC (MRID 42973501) did not alter the original findings of renal carcinoma (HED # 011031)

Based upon the decreases in body weights, food consumption and food efficiency, and the increased incidence of liver lesions, the highest dose tested (1000 mg/kg/day) had reached the maximum tolerated dose (MTD). In addition, the 1000 mg/kg/day is also considered as the upper limit for an oncogenicity study according to the policy of the HED (Memorandum of Farber to Tox Branch, 7/27/88). The **LOAEL** for chronic toxicity was 250 mg/kg/day based on decreases in the absolute and relative kidney weights in males and females and the **NOAEL** is 65 mg/kg/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements for a combined chronic toxicity/carcinogenicity in the rat [OPPTS 870.4300 [§83-5]; OECD 453]

870.4200b: Carcinogenicity (feeding) - Mouse

In a carcinogenicity study (MRID 42100102), MGK Repellent 326 (100% purity was reported for this lot in MRID 42400101; Lot #: 3716) was administered for up to 80 weeks to 50 CD-1 mice/sex/dose in the diet at nominal dose levels of 0, 0, 125, 500, or 2000 mg/kg/day (2 x limit dose).

No treatment-related effects were noted during clinical observations, ophthalmoscopic examinations, or hematological examination. No adverse effect was observed in the 125

mg/kg/day group.

General signs of toxicity were observed at 500 and 2000 mg/kg/day. There was an equivocal effect on the mortality of the 2000 mg/kg/day males where minor to slight increases (incr 9-16%) were observed; however, the effect was not dose-dependent at Week 78. Survival exceeded guideline requirements for an acceptable study. In general, body weights were decreased ($p<0.05$) relative to both concurrent controls in the 500 (decr 3-14%) and 2000 (decr 4-24%) mg/kg/day groups beginning at Week 2 (or Week 40 for the 500 mg/kg/day females), and these decreases persisted until the end of the study. Decreases in cumulative body weight gains were observed in the 500 and 2000 mg/kg/day groups at Weeks 0-2 (decr 33-50 and 100-200%, respectively) and 0-78 (decr 27-43 and 50-63%, respectively). Increased food consumption was observed in the 2000 mg/kg/day group (incr 3-41%; $p<0.05$) generally from Week 5 until study termination. Changes ($p<0.05$) were observed in the reported food efficiencies in all treated groups; however, these changes were sporadic and unrelated to treatment. Nevertheless, body weight gains decreased in the 2000 mg/kg/day group while food consumption increased, which suggested decreased food efficiency.

In the combined animals (n=50), at 500 and 2000 mg/kg/day, the liver was adversely affected in both sexes, and the gall bladder was adversely affected in males. Liver/gallbladder (relative to body) organ weights were increased in both sexes at 500 and 2000 mg/kg/day (incr 7-47% in males and incr 78-113% in females; dose-dependent; $p<0.05$). At 2000 mg/kg/day, liver nodules (gross) were observed in the males (22% treated vs 2-12% controls) and females (32% treated vs 2-4% controls). Liver masses (gross) were observed in the 2000 mg/kg/day males (14% treated vs 4-8% controls). At 2000 mg/kg/day, the following increased incidences were observed: (i) histiocytosis (trace to mild; 62-68% treated vs 0-20% controls) in both sexes; (ii) hypertrophy (trace to moderate; 8-24% treated vs 0% controls) in both sexes; (iii) hyperplastic nodules (10-14% treated vs 0-4% controls) in both sexes; (iv) portal bile duct proliferation (trace to moderate; 22-42% treated vs 0-2% controls) in both sexes; (v) portal mononuclear cell infiltrate (trace to moderate; 38-78% treated vs 2-4% controls) in both sexes; (vi) bile stasis (trace to severe; 58% treated vs 0% controls) in males; (vii) spongiosis hepatitis (trace to moderate; 20% treated vs 0% controls) in males; and (viii) calculus (trace to severe; 52% treated vs 0% controls) in females. Additionally, an increased incidence of histiocytosis in the liver of 500 mg/kg/day males was observed (22% treated vs 0-6% controls). An increased incidence of gallbladder calculus was observed in the 2000 mg/kg/day males (46% treated vs 0% controls).

Slight effects were seen in the reproductive system of the 2000 mg/kg/day males. Decreased testes (absolute and relative to brain; decreased 25-30%; $p<0.01$) weights were observed. Also, increased incidences and severity of relative aspermia in the epididymis (mild to severe; 32% treated vs 6-14% controls), aspermatogenesis in the testes (trace to severe; 38% treated vs 22-32% controls), and interstitial cell hyperplasia (mild to severe; 10% treated vs 0-2% controls) were observed.

In the combined animals, lung nodules were observed macroscopically in the 2000 mg/kg/day males (32% treated vs 16% controls).

Increased chronic nephritis (trace to severe; 68-72% treated vs 50-54% controls) was observed in the 500 and 2000 mg/kg/day females; however, the severity was not dose-dependent (severe grade: 6-8% treated vs 10-14% controls). Therefore, this was regarded as an equivocal effect.

Under the conditions of this study, dosing is considered adequate to assess the carcinogenic potential of MGK Repellent 326 based on decreased body weights and body weight gains in both sexes, increased liver/gall bladder weights in both sexes, and increased liver histiocytosis in males observed at 500 and 2000 mg/kg/day.

The LOAEL is 500 mg/kg/day based on decreased body weights and body weight gains in both sexes, increased liver/gall bladder weights in both sexes, and increased liver histiocytosis in males. The NOAEL is 125 mg/kg/day.

In the liver of 2000 mg/kg/day females (n=50), an increased incidence (p#0.001 compared with both controls; Life Table Test, Incidental Tumor Test, and Fisher's Exact Test) of adenomas (26% treated vs 0% controls) was observed. Positive dose-response trends were detected (p=0.000), and the incidence of adenomas exceeded the historical control range of 0-3.33%. Corroborating non-neoplastic pathological evidence of proliferation was observed. In the combined females (n=50) at 2000 mg/kg/day, liver nodules (gross) were observed (32% treated vs 2-4% controls). Microscopically, hyperplastic nodules (10% treated vs 0-2% controls) and portal bile duct proliferation (trace to mild; 42% treated vs 0-2% controls) were observed.

An increased incidence (p#0.003 compared with both controls; Life Table Test, Incidental Tumor Test, and Fisher's Exact Test) of alveolar bronchiolar adenomas (48% treated vs 20% controls) was observed in the 2000 mg/kg/day males (n=50). Positive dose-response trends were detected (p=0.000), and the incidence of adenomas exceeded the historical control range of 0-31.67%. Following examination of the lung sections, additional lung sections were made. Microscopic examination of these additional sections demonstrated an increased incidence (p#0.050 compared with Control A, and p#0.111 compared with Control B; Fisher's Exact Test) of alveolar bronchiolar adenomas (48% treated vs 30-34% controls). The incidence of adenomas remained in excess of the historical control range. The incidence of alveolar adenoma in Control B (34%) also exceeded the historical control range; thus, Control A would be most appropriate for Fisher's Exact Test comparison. In the combined animals (n=50), lung nodules were observed macroscopically in the 2000 mg/kg/day males (32% treated vs 16% controls).

Under the conditions of this study, the carcinogenic potential of MGK Repellent 326 is positive at 2000 mg/kg/day (2x the limit dose). Increased incidences of liver adenomas in females and alveolar bronchiolar adenomas in males were observed.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements [OPPTS 870.4200; OECD 451] for a carcinogenicity study in mice.

4.7 Mutagenicity

Adequacy of data base for Mutagenicity: The MGK® Repellent 326 data base for Mutagenicity is considered adequate based on pre 1991 and 1991 mutagenicity guidelines.

The HIARC concluded that there is no concern for mutagenicity resulting from exposure to MGK® Repellent 326. MGK® Repellent 326 was negative in a bacterial reverse mutation assay with and without microsomal activation (MRID 40382101). It did not cause chromosomal aberrations in CHO cells (MRID 40382102), or induce mutations in mouse lymphoma cells (MRID 40382104). It did not induce unscheduled DNA synthesis in primary rat hepatocytes (MRID 40555201, 41255601).

Gene Mutation

GLN 870.5100, MRID 40382101 Acceptable, pre 1991 guidelines Tested at up to cytotoxic doses.	No mutagenic effect was noted with or without microsomal activation at concentrations up to the toxic range of 5000 micrograms of MGK® Repellent 326/plate in the initial tests or in the confirmatory assay.

Chromosomal Aberrations

GLN 870.5300 , MRID 40382102 Acceptable, pre 1991 guidelines	*In Vitro* mammalian cell gene mutation - CHO/HGPRT forward mutation assay. MGK® Repellent 326 was negative for the induction of structural chromosome aberrations in the duplicate assays in the presence and absence of metabolic activation (MA) up to toxic dose levels (0.2 uL/mL without MA; 0.5 and 1.0 uL/mL with MA)

GLN 870.5300, MRID 40382104 Acceptable, pre 1991 guideline	*In Vitro* mammalian cell gene mutation - L5178Y TK+/- Mouse Lymphoma Mutagenesis Assay. MGK® Repellent 326 was tested up to cytotoxic levels (>0.18 µL/mL, -S9 and >0.24 µL/mL, +S9). Increases in mean mutant frequency of at least 2x background with >10% growth were observed in the absence (0.18 µL/mL, trial 4) and presence (1.0 µL/mL, trial 1; 0.9 and 1.2 µL/mL, trial 2) of S9-activation; however, because the results were not reproducible (-S9) and there was no clear dose-response observed in any trial (+ or -S9), the results of the study are considered equivocal

Other Mehanisms

GLN 870.5550, MRID 40382103 Acceptable. Pre 1991 guideline	Unscheduled DNA synthesis in Rat Primary Hepatocytes. MGK® Repellent 326 was tested up to cytotoxic levels (0.06 µL/mL) as determined by increased levels of lactic acid dehydrogenase (LDH) activity. No significant increases in mean net nuclear grains (NNG) or percent cells in repair were observed compared to controls. The positive control, dimethylbenz(a)anthracene (DMBA), induced the appropriate response.

4.8 Neurotoxicity

Adequacy of data base for Neurotoxicity:

There are no neurotoxicity studies available but the chronic and subchronic studies do not indicate neurotoxic effects by this chemical. Toxic effects of MGK 326 noted in chronic studies in rats (MRID 42093902), mice (MRID 42100102) and dogs (MRID 42320602) and subchronic studies in rats (MRID 42093901) and mice (MRID 42100101) are decreased body weights and body weight gains. No toxic effects were noted in a 90-day inhalation study in rats at the highest

doses tested of 0.324 mg/L. In a developmental study, MGK® Repellent 326 caused mortalities in rabbits treated at 350 mg/kg/day (MRID 40433301). There was a low incidence of clinical signs in some of the dying animals: leaning to the left, labored breathing, involuntary eye movement, dry white material in nasal area, decreased motor activity, and no righting reflex. These clinical signs of toxicity were considered by HIARC to be **agonal** and not indicative of frank toxicity. Several animals that died or were sacrificed *in extremis* displayed no clinical signs of toxicity. At the next lower dose there were no effects and was considered to be the NOAEL for maternal toxicity.

4.9 Metabolism

Adequacy of data base for metabolism: The data base for MGK® Repellent 326 metabolism is considered to be complete. No additional studies are required at this time.

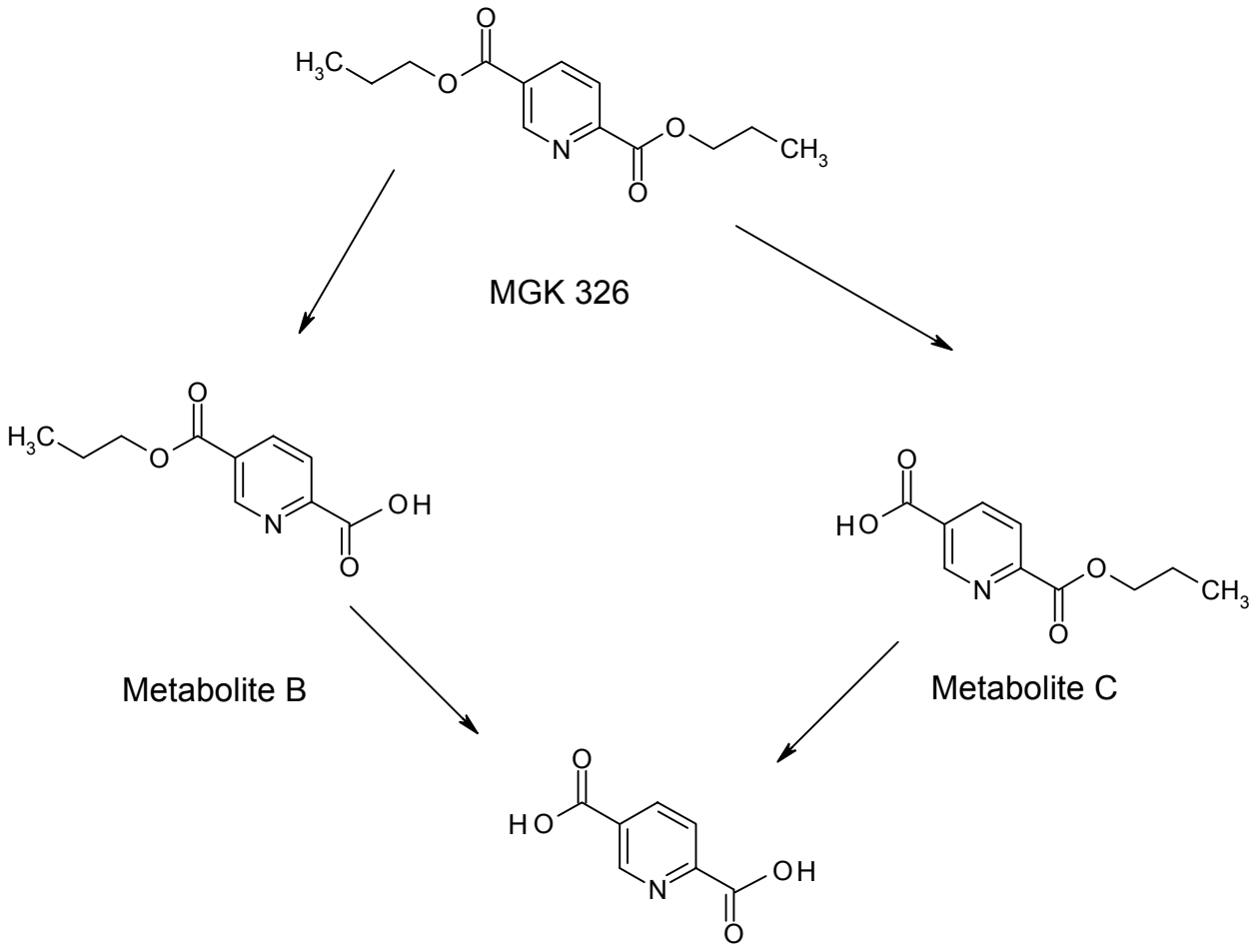
In a metabolism study to determine the metabolic breakdown of pyridine ring to $^{14}CO_2$, MGK® Repellent 326 (lot # 3716, purity 99.7%) mixed with pyridine-4-^{14}C- MGK® Repellent 326 (radiochemical purity 99.6%) was administered in corn oil as a single oral dose by gavage to two rats/sex at a dose of 105 mg/kg body weight. Expired air was trapped in a gas trap containing 2:1 mixture of ethanolamine and cellosolve and aliquots were measured for radioactivity. None to a negligible amount (<0.02% in the males and <0.04% in the females) of the ^{14}C in the pyridine ring of the parent compound was metabolized to $^{14}CO_2$. (MRID 42246501)

In another study in rats, pyridine-4-^{14}C- MGK® Repellent 326, administered orally (100 mg/kg body weight), was absorbed rapidly and reached a peak blood level at 30 minutes and 45 minutes after dosing in male and females rats, respectively. The blood radioactivity dropped sharply afterwards with a half life of 1.5 hours. The orally administered pyridine-4-^{14}C- MGK® Repellent 326 was also rapidly absorbed and eliminated from the body, mainly in the urine. About 89 - 99% of the administered dose was eliminated within 12 hours of dosing. Fecal excretion was minimal and accounted for 1-3% of the administered dose. All of the fecal excretion of the radioactivity occurred after the first 12 hours of dosing. Residual radioactivity in the tissues after 168 hours was nil to insignificant. There were no differences between males and females regarding the elimination pattern of the radioactivity. There were no apparent differences between single (100 mg/kg body weight) or oral multiple dosing (a single oral dose of 100 mg/kg body weight of the labeled compound following two weeks of daily dosing of 100 mg/kg/day with the non-radiolabeled compound). At higher doses (a single oral 1000 mg/kg dos), the elimination of the radioactivity appeared to be slower than in single lower oral dose (100 mg/kg). The slower urinary elimination seen in the high dose group males and females might be limited by either absorption or metabolism. The elimination of the radioactivity was much faster following single iv dosing (100 mg/kg); 87- 89% of the administered dose was eliminated during the first 4 hours. The fecal excretion was less than 1.3% of the administered iv dose. (MRID 42305701)

Major (>10%) urinary metabolites from the absorption, distribution and excretion study (MRID 42305701) were isolated, purified, identified and quantified. Analysis of radioactive residues in male and female rat urine by HPLC revealed no difference in metabolic profiles. The radioactive residue was separated by HPLC into a major (Metabolite A) and minor peak (Unknown 1). The parent compound was not detected in the urine samples. Metabolite A fraction was further purified, concentrated and analyzed with mass spectrometry (MS) and identified as the dicarboxylic acid derivative of MGK Repellent 326. Approximately, 95% - 99% of the radioactivity in the urine from pooled male and female rats from various dose groups was associated with Metabolite A. The minor metabolite represents maximally 4.5% of the radioactivity in the urine. Approximately, 88% - 97% of the administered pyridine-4-^{14}C-MGK® Repellent 326 was metabolized to Metabolite A while less than 4.2% of the administered dose was converted to Unknown 1. Based upon these results, it was postulated that the parent compound was hydrolyzed at the two ester sites to form the dicarboxylic acid derivative of MGK Repellent 326. (MRID 42246502).

In a special metabolism study in humans, MGK® Repellent 326 (lot # 3716-1, purity 99.5%) mixed with pyridine-4-^{14}C- MGK® Repellent 326 (radiochemical purity 99.0%) was administered orally in capsules (taken with 200 ml of water) to two adult, healthy, male consenting (written consent) human volunteers (fasted 10 hours prior to dosing and 4 hours after dosing except for water) as a single dose of 500 mg/subject (approximately 6.1-6.8 mg/kg, 95.1 uCi). No toxicity signs were noted. Serum clinical chemistry screen and urinalysis screen were normal. Peak radioactivity blood levels were attained at 2 and 4 hours with a plasma half-life of 5.3-8.0 hours. The test compound was rapidly absorbed from the gastrointestinal system and eliminated in the urine (41.5% - 54% during the first 8 hours). Urinary excretion of the radioactivity was completed largely within the first 36 hours after dosing (81.9-85.1% of the AD). Total urinary excretion of the radioactivity amounted to 82.3-85.8% of the AD by 128 hours after dosing. Excretion of the radioactivity in the feces was minimal and occurred mostly within the first 6 hours after dosing (1.87% - 2.61% of the AD). The total recovered radioactivity in the urine and feces after 128 hours of dosing was 84.7 and 88.4% of the AD in both subjects. The balance of the AD was not accounted for. The HPLC analysis of the 0-24 hour composited urine of the two volunteers revealed three metabolites with no parent compound present. These were identified by mass spectrometric (MS) analysis as the hydrolysis products of the parent material. These were Metabolite A: the diacid of MGK 326 (39.8% of the urinary radioactivity), Metabolite B ; 5-carboxy unesterified (3.9% of the urinary radioactivity) and Metabolite C: 2-carboxy unesterified (40.3% of the urinary radioactivity). Metabolites B and C were converted to Metabolite A by acid hydrolysis. A metabolic chart based on these findings is presented below. (MRID 43099401).

Appendix: Proposed Metabolic Pathway of MGK 326 in Humans Dosed Orally



870.7600: Dermal Absorption - Rat

In a dermal absorption study (MRID 42246503), MGK® Repellent 326 (lot # 3716-1, purity 99.5%) mixed with pyridine-4-^{14}C- MGK® Repellent 326 (radiochemical purity 99%) was applied dermally to a group of 5 male, 8 weeks old fasted CD rats to the shaven skin back areas (2.5 x 5 cm). Each rat received a single dermal application of 4 mg/kg (0.08 mg/cm^2) of the test material dissolved in isopropanol. The radioactivity levels in the blood of these rats was determined as a function of time over a 168 hour period by collecting blood from the tail vein. In another experiment, four groups of male rats (5/group) were prepared and treated similarly with a single dermal application of 2.5 mg/kg (0.06 mg/cm^2). These were sacrificed at time intervals corresponding to radiolabeled residues at peak blood levels (1 hr), at half-life (10 hrs), at second half-life (19 hrs), and 168 hours after administration as determined from the first experiment. Blood samples from these groups were collected by heart puncture. Samples of urine, feces, tissues and skin and cage washes were collected for analysis of radioactivity. The test material was absorbed through the skin and rapidly reached a peak blood level (13% of the administered dose) at 1 hour after dosing and gradually declining reaching a plateau level after 24 hours. The study author calculated a first half life of 9 hours and a second half life of 19 hours.
Mean dermal absorption of radiolabeled MGK-326 (the sum of radioactivity in urine (major amount), feces, tissues/carcass, and cage wash) after 10 hours of exposure was 45%. Mean recoveries of the test material ranged from (95-103%). The majority of recovered test material was found in the skin rinse at the 1 and 10 hr time intervals (86 and 53% respectively). Mean amounts of test substance found in the skin rinse decreased significantly at the 19 and 168 hr time intervals (31 and 7% respectively) indicating that material remaining in/on the skin continues to be absorbed over time.

4.10 Special/Other Studies

a. Published Studies. No published studies were available.

b. Dermal Absorption - Humans. There are three dermal absorption studies available in humans. One was conducted with the technical material and the other two were conducted using the formulated material.

In a non-guideline dermal absorption study (MRID 42974601), four healthy human volunteers (74.4-91.7 kg and age ~ 21 years) were exposed to pyridine-4-^{14}C-MGK® Repellent 326 (non-radiolabeled lot # 3716, purity 99.7%; radiolabeled code: CFQ 5947, radiochemical purity 99%) by a single dermal application of 100 ul of the test solution in isopropyl alcohol at an approximate dose of 0.012 mg/kg (41.7 ug/cm^2) to the test site (4x6 cm section of the volar area of the right or left forearm). The application site was covered for 8 hours. After 8 hours of exposure application sites were cleaned with cotton swabs soaked in isopropyl alcohol and rinsed with isopropyl alcohol. The application site was then covered with a gauze pad. At 1, 23,

and 45 hours after removal of the test material, tape stripings were performed on the application site and were measured for radioactivity. The subjects were confined to the testing facility for 6 days for observations and sample collections. Urine and feces were collected at intervals throughout the study period for up to 128 hours after application of the dose. Plasma radioactivity levels indicated that ^{14}C-MGK® 326 was steadily absorbed through the human skin, and a peak plasma concentration was reached when the exposure was terminated at 8 hours. **Mean dermal absorption of radiolabeled MGK-326 (sum of radioactivity in urine and feces) from an 8 hr exposure was 24.9% (cumulative total measured over 128 hrs).** Absorbed radioactivity was eliminated mainly in the urine (24.7% of the applied dose) and only negligible amounts were eliminated in the feces. The majority of unabsorbed dose was found in the isopropanol wash (48.5%). Mean total recovery of applied dose was 95.5%.

In a second non-guideline dermal absorption study (MRID 42974602), four healthy human volunteers (61.1-79.3 kg and age ~ 22 years) were exposed to formulated pyridine-4-^{14}C-MGK® Repellent 326 (non-radiolabeled lot # 3716, purity 99.7%; radiolabeled code: CFQ 5947, radiochemical purity 99%) by a single dermal application of 100 ul of the test solution in isopropyl alcohol at an approximate dose of 0.014 mg/kg (46.6 ug/cm^2) to the test site (4x6 cm section of the volar area of the right or left forearm). The dose formulation contained 1.01% (w/w) MGK-326 (0.7% ^{14}C-MGK® Repellent 326:0.31% non-radiolabeld MGK-326), 17.5% (w/w) DEET (lot# A-1-96, purity 98.8%), and 5% (w/w) MGK® 264 (lot # 3843, purity 100%). The material was left in place under a protective cover for 8 hours. After 8 hours of exposure, the protective cover was removed and the application sites were cleaned with cotton swabs soaked in isopropyl alcohol and rinsed with isopropyl alcohol. The application site was then covered with a gauze pad. At 1, 23, and 45 hours after removal of the test material, tape strippings were performed on the application site and were measured for radioactivity. The subjects were confined to the testing facility for 6 days for observations and sample collections. Urine and feces were collected at intervals throughout the study period for up to 128 hours after application of the dose. Plasma radioactivity levels indicated that the formulated ^{14}C-MGK® 326 was continuously absorbed through the human skin, and a peak plasma concentration was reached when the exposure was terminated. Plasma radioactivity levels dipped after isopropanol wash. **Mean dermal absorption of radiolabeled MGK-326 (sum of radioactivity in urine and feces) from an 8 hr exposure was 3.4% (cumulative total measured over 128 hrs)**. Absorbed radioactivity was eliminated mainly in the urine and only negligible amounts were eliminated in the feces. The majority of unabsorbed dose was found in the isopropyl alcohol swabs (78%). Mean total recovery of applied dose was 102.17%.

In a third non-guideline multiple-dose dermal absorption study (MRID 42732101), four healthy male human volunteers (81.3 ± 2.9 kg and age 22 ± 3.6 years) received daily by dermal application 100 ul solution (in isopropanol) of unlabeled MGK 326 (1% w/w, lot 3716, purity 99.7%) formulated with both DEET (17.5% w/w, lot# A-1-96, purity 98.8%) and MGK 264 (5% w/w, lot # 3843, purity 100%) at a dose of ~0.012 mg/kg/day (0.042 mg/cm^2) for 14 days. After each application the site was covered for 8 hours after which the protective cover was removed

and the site was washed with soap and water and marked for subsequent applications. On the 15th day a similarly formulated dose of pyridine-4-^{14}C- MGK® Repellent 326 (radiolabel code CFQ 5947, radiochemical purity 99%) was applied. One subject was withdrawn from the study on day 14 because of a superficial skin trauma, not related to the study material. After 8 hours of exposure to the radiolabeled material, the protective cover was removed and saved for analysis. The application sites were cleaned with cotton swabs soaked in isopropanol and then rinsed with isopropyl alcohol. The application site was then covered with a gauze pad. At 1, 23, and 45 hours after removal of the test material, tape strippings were performed on the application site and were measured for radioactivity. The subjects were confined to the testing facility for a total of 20 days for test material applications, observations, and sample collections. Urine and feces were collect at intervals throughout the study period for up to 128 hours after application of the radiolabeled dose. Plasma radioactivity levels indicated that the formulated ^{14}C-MGK® 326 was continuously absorbed through the human skin, and peaked when the exposure was terminated. The plasma radioactivity levels as a function of time were analogous to those obtained with single dose dermal application of the pure material (MRID 42974601) and the formulated material (MRID 42974602).

Mean dermal absorption of radiolabeled MGK-326 (sum of radioactivity in urine and feces) from an 8 hr exposure was 4.75% (cumulative total measured over 128 hrs). Absorbed radioactivity was eliminated mainly in the urine and only negligible amounts were eliminated in the feces. The majority of unabsorbed dose was found in the isopropyl alcohol swabs (79%). Mean total recovery of applied dose was 99.28.

5.0 HAZARD ENDPOINT SELECTION

On October 15, 2002, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) reviewed the toxicology database for MGK® Repellent 326 with regard to the toxicological endpoint selection for use as appropriate in risk assessments. MGK® Repellent 326 is formulated as an insect repellent used in companion animal health care (pets and horses) and personal use. There are no proposed or registered food uses. The potential for increased susceptibility of infants and children from potential exposure to MGK® Repellent 326 was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document.

5.1 Endpoint Selection Table.

See Section 9.2 for Endpoint Selection Table.

5.2 Dermal Absorption

When all the above studies are considered, the most likely dermal absorption factor would be the one derived from human volunteer studies. MGK® Repellent 326 for personal use is always used in formulations with MGK 264 and DEET. Therefore the studies with the formulated material

would be most appropriate (MRID 42732101 and MRID 42974602). In these studies the dermal absorption after an 8 hour exposure period ranges from 3.4% to 4.75%. Using the upper end of the range, a dermal absorption factor of 5 % is proposed.

5.3 Classification of Carcinogenic Potential

The HED Carcinogenicity Peer Review Committee (CPRC) classified MGK® Repellent 326 as Group B2 - probable human carcinogen with an inadequate evidence in humans (HED memo July 21, 1993). This decision was based on the finding of multiple malignant and benign tumors in the rat and in the mouse. A Q_1^* based on liver adenomas, carcinomas and combined adenomas/carcinomas in rats was derived (using 3/4 scaling factor) to be 1.63×10^{-3} $(mg/kg/day)^{-1}$ in human equivalents for the male rat and 1.2×10^{-3} $(mg/kg/day)^{-1}$ in human equivalents for the female rat. The registrant rebutted this classification and requested a second peer review of the carcinogenicity data based on a re-read of the histological slides by a consultant pathologist. However, for the reconsideration of the previous CPRC cancer classification, the revised pathology diagnosis should be the consensus of a pathology peer review group similar to that employed by the NTP according to Pesticide Regulation (PR) Notice 94-5 dated August 24, 1994. There is no record that such a pathology peer review group had been convened.

6.0 FQPA CONSIDERATIONS

The HIARC concluded that the toxicology database for MGK® Repellent 326 is adequate for FQPA considerations.

6.1 Special sensitivity to Infants and Children

The HIARC concluded that there is low concern (and no residual uncertainty) for pre- and/or postnatal toxicity resulting from exposure to MGK® Repellent 326. The available data provided no indication of increased susceptibility (quantitative or qualitative) of rats or rabbits to *in utero* exposure to MGK Repellent 326. However, there is quantitative evidence of increased susceptibility in the 2-generation reproduction study in rats characterized as decreased pup body weight at dose lower (250 mg/kg/day) than that causing parental effects (1000 mg/kg/day). In addition, the effects observed in the offspring at 1000 mg/kg/day (pup death) in this study are more severe than those seen in parental animals (decreased body weight, body weight gain, and food consumption; and liver histopathology changes in males and females) which presents qualitative evidence of increased susceptibility at the highest dose level. Since there is evidence of increased susceptibility in the 2-generation reproduction study in rats with MGK Repellent 326, the HIARC performed a degree of concern analysis for the effects seen and evaluated residual uncertainties when considered in context of all available toxicity data. The HIARC determined that there is a low degree of concern (and no residual uncertainty) for the quantitative susceptibility in rat reproduction study because: 1) it is a well conducted study with adequate dosing; 2) there is a well defined pup NOAEL (for the decrease in pup body weight); 3) there is

good dose-response for pup effects; and 4) the decrease in pup body weight occurred late during lactation (Days 14-21) when the pups are probably eating significant amounts of feed. In addition, the HIARC determined that there is a low degree of concern (and no residual uncertainty) for the qualitative susceptibility seen at the highest dose (1000 mg/kg/day) in rat reproduction study because: 1) the more severe pup effects are occurring at the limit dose; 2) in the presence of marked parental effects; and 3) at a much higher dose than that which is selected for regulation and risk assessment (NOAEL = 65 mg/kg/day; LOAEL = 250 mg/kg/day).

Since MGK Repellent 326 is not registered for use in/on foods and has no published or proposed tolerances, the special FQPA safety factor is **not applicable** to risk assessments for this chemical.

6.2 Recommendation for a Developmental Neurotoxicity Study (DNT)

The HIARC concluded that a developmental neurotoxicity study is not required since there was no evidence of neurotoxicity or neuropathology from the available studies and there is no concern or residual uncertainties for pre/post-natal toxicity.

7.0 OTHER ISSUES: None

8.0 REFERENCES

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9.0 APPENDICES
Tables for Use in Risk Assessment

9.1 Toxicity Profile Summary Tables

9.1.1 Acute Toxicity Table - *See Section 4.1*

9.1.2 Subchronic, Chronic and Other Toxicity Table

TOXICOLOGY PROFILE
MGK 326, TECHNICAL GRADE
September 30, 2002

MGK 326: Chronic Studies

GL #	MRID	Study Type	Results and Classification
83-5 870.4300	42093902 42973501	24-Month Combined Chronic/Carcinogenicity Feeding-Rats, Sept. 30, 1991 100% a.i. 0, 0, 65, 250 or 1000 mg/kg/day	**LOAEL** = 250 mg/kg/day based on decreases in the absolute and relative kidney weights in males and females **NOAEL** = 65 mg/kg/day. At 1000 mg/kg/day (upper limit dose), the test compound produced increases in the incidence of liver and renal cell tumors. Body weights, food consumption and food efficiency were significantly decreased in males and females at this dose. **Acceptable/guideline**
83-2b 870.4200b	42100102	18-Month Carcinogenicity in Mice, Sept. 30, 1991 100% a.i. 0, 0, 125, 500, or 2000 mg/kg/day (2 x limit dose).	**LOAEL** = 500 mg/kg/day based on decreased body weights and body weight gains in both sexes, increased liver/gall bladder weights in both sexes, and increased liver histiocytosis in males. **NOAEL** = 125 mg/kg/day At 2000 mg/kg/day, the test compound increased incidences of liver adenomas in females and alveolar bronchiolar adenomas in males. **Acceptable/guideline**
83-1b 870.4100	42320602	12-Month Chronic Oral Toxicity (dietary) - Dogs September 19, 1989 99.5% a.i. 0, 250, 1,000 or 4,000 ppm (0, 8.27, 34.3, or 148.0 mg/kg/day for males; 0, 8.12, 34.1 or 117.5 mg/kg/day for females) 2-month Range Finding Study: 0, 4,000, 7,500, 15,000/10,000; 30,000/1,000 or 60,000/2,000 ppm	**Main Study** **LOAEL =** 4,000 ppm (148.0 mg/kg/day) based on the inhibition of body weight gain **NOAEL** = 1,000 ppm (34.3) mg/kg/day. **Range Finding Study** At $ 7500 ppm : marked decrease in body weights and food consumption, a decrease in the liver and kidney weights, liver histological changes (centrilobular hypertrophy, bile duct proliferation and portal fibrosis). At 15,000/10,000 ppm: marked increase in alanine transferase activity in both sexes, a slight decrease in the testicular weights of males and in the ovarian weights of females. **Acceptable/guideline**

MGK 326: Sub-chronic Studies

GL #	MRID	Study Type	Results and Classification
82-1 870.3100	42093901	90-Day Dietary Study in Rat, October 24, 1991 100% a.i. 0, 125, 250, 500, 1000 or 2000 mg/kg/day	**LOAEL** = 1000 mg/kg/day, based on the reduction in body weights in both sexes, and organ weight decreases in males. **NOAEL** = 500 mg/kg/day **Acceptable/Guideline**
82-1 870.3100	42100101	90-Day Dietary Range Finding Toxicity Study - Mice. October 24, 1991 100% 0, 125, 250, 500, 1000, or 2000 mg/kg/day)	**LOAEL** = 2000 mg/kg/day based on decreased body weights and body weight gains and increased food consumption and liver (mild tan foci-multilobular) and kidney (mild white focus-unilateral) effects observed in males. **NOAEL** = 1000 mg/kg/day **Acceptable/Guideline** (when considered with MRID 42100102)
82-4 870-3465	42990201	90-Day Inhalation Toxicity Study - Rat. April 2, 1993. 100% a.i. 0, 0.0105, 0.028, 0.095, or 0.324 mg/L for 6 hours/day, 5 days/week	**LOAEL** = >0.324 mg/L (60 mg/kg/day) for systemic effects based on the lack of toxic effects. **NOAEL** = 0.324 mg/L (60 mg/kg/day). **Acceptable/Guideline**
82-2 870.3200	42427202	90 - Day dermal toxicity - rabbits. July 16, 1992 100% a.i. 0, 10, 30 or 100 mg/kg/day, 6 hours/day, 7 days/week.	**LOAEL** = 100 mg/kg/day for dermal effects based on fissuring and moderate skin reactions and the **NOAEL** is 30 mg/kg/day. **LOAEL** = >100 mg/kg/day for systemic effects based on the lack of toxic effects and the **NOAEL** is 100 mg/kg/day. **Acceptable/Guideline**

MGK 326: Developmental Studies

GL #	MRID	Study Type	Results and Classification
83-3a 870.3700	41987802	Developmental Toxicity-Rat: April 6, 1991 100% 0, 100, 300 or 1000 mg/kg/day Range Finding 0, 100, 200, 400, or 800 mg/kg/day	**Maternal Toxicity** **LOAEL** = 1000 mg/kg/day based on reduced body weight gain (14.5% decrease; $p<0.01$) during GD 6-15. **NOAEL** is 300 mg/kg/day. **Developmental Toxicity** **LOAEL** = >1000 mg/kg/day (the highest dose tested; the **NOAEL** is 1000 mg/kg/day **Acceptable/guideline**
Non-Guideline	45682901	Range finding teratology study - Rabbit, August 28, 1986. 100% purity, orally via gavage at 0, 125, 250, 500, 1000 or 2000 mg/kg/day (5 females/group) on gestation days 7 through 19.	Mortality occurred at the 500, 1000, and 2000 mg/kg/day group (60%, 100%, 100%, respectively). The surviving animals were comparable to control animals in behavior and appearance. The mean number of viable fetuses, postimplantation loss, total implantations and corpora lutea of the 125 and 250 mg/kg /day groups were comparable to those of the controls. Doses of 35, 100, and 350 mg/kg/day were selected (MRID 40433301) for developmental toxicity study. This study is **acceptable** for the purpose it was designed for.
83-3b 870.3700	40433301	Developmental Toxicity-Rabbit: Oct. 29, 1987. 100% purity 0, 35, 100, or 350 mg/kg/day	**Maternal Toxicity** **LOAEL** = 350 mg/kg/day, based on mortality preceded by decreased body weight gain. Low incidence of clinical signs: leaning to the left, labored breathing, involuntary eye movement, dry white material in nasal area, decreased motor activity, and no righting reflex. several animals that died or were sacrificed *in extremis* displayed no clinical signs of toxicity. **NOAEL** = 100 mg/kg/day. **Developmental Toxicity** **LOAEL** = was not observed. Due to high mortality in the 350 mg/kg/day does, fetal toxicity at this dose could not be evaluated. No fetal toxicity was observed at 35 or 100 mg/kg/day. **NOAEL** = 100 mg/kg/day. **Acceptable/guideline**

83-4 870.3800	41547801	2-Generation reproduction-Rat, June 7, 1990, 100% purity dietary dose levels of 0, 65, 250 or 1000 mg/kg/day	**Parental Toxicity** **LOAEL** = 1000 mg/kg/day based on decreased body weights, body weight gains, and food consumption and histopathological liver changes in the males and females (trace to mild biliary stasis and portal bile duct proliferation in F_0 females. Trace to mild portal bile duct proliferation and trace portal mononuclear cell infiltrates in the F_1 males and females) **NOAEL** = 250 mg/kg/day **Offspring Toxicity** **LOAEL =** 250 mg/kg/day based on decreased pup body weight. At 1000 mg/kg, increased deaths in F_1 pups relative to controls during PND 0-4 and PND 4 through 21 and the F_2 pups during PND 4 through 21 were noted. **NOAEL** = 65 mg/kg/day. **Acceptable/guideline**

MGK 326: Metabolism and Absorption Studies

GL #	MRID	Study Type	Results and Classification
85-1 870-7485	42305701	Metabolism- ADME Study - Rat May 11, 1990 pyridine-4-^{14}C- MGK® Repellent 326 used. 1) single oral 100 mg/kg for blood collection over 14 hour period. 2) single oral 100 **or** 1000 mg/kg/day **or** single iv dose of 1 mg/kg and held 168 h. 3) daily oral dosing 100 mg/kg of unlabeled compound for 14 days followed by a single oral dose of labeled 100 mg/kg and held for 168 h.	Pyridine-4-^{14}C- MGK® Repellent 326, administered orally, was absorbed rapidly and reached a peak blood level at 30 minutes and 45 minutes after dosing in male and females rats, respectively. Its blood half life was 1.5 hours. About 89 - 99% of the administered dose was eliminated within 12 hours of dosing, mainly in the urine. Fecal excretion was minimal and accounted for 1-3% of the administered dose (occurred after the first 12 hours of dosing). Residual radioactivity in the tissues was nil to insignificant. There were no differences between males and females or between single oral or multiple dosing regarding the elimination pattern of the radioactivity. In the single high dose group, the elimination of the radioactivity appeared to be slower than the other groups. In the iv dosing, the elimination of the radioactivity was much faster; 87- 89% of the administered dose was eliminated during the first 4 hours. The fecal excretion was less than 1.3% of the administered iv dose. **Acceptable/guideline**
85-1 870-7485	42246502	Metabolism - Identification of Metabolites - Rat. Addendum to MRID 42305701	HPLC metabolic profiles of male and female rat urine were similar. HPLC analysis revealed a major peak (Metabolite A: 95-99% of the urinary radioactivity) and a minor peak (Unknown 1; up to 4.5%). The parent compound was not detected in the urine samples. Metabolite A fraction was further purified, concentrated and analyzed with mass spectrometry (MS) and identified as the dicarboxylic acid derivative of MGK Repellent 326. Based upon these results, it was postulated that the parent compound was hydrolyzed at the two ester sites to form the dicarboxylic acid derivative of MGK Repellent 326. **Acceptable/guideline**
85-1 870-7485	42246501	Metabolism - determination of expired CO_2 - Rat August 20, 1990. Pyridine-4-^{14}C- MGK® Repellent 326 used. Single oral dose 105 mg/kg	None to a negligible amount (<0.04%) of the ^{14}C in the pyridine ring of the parent compound was metabolized to $^{14}CO_2$. **Acceptable/guideline**

Non-Guideline	43099401	Metabolism Study - Humans December 15, 1993 Pyridine-4-^{14}C- MGK® Repellent 326 used 6.1-6.8 mg/kg; 95.1uCi 2 adult healthy males	Peak radioactivity blood levels were attained at 2 - 4 hours with a plasma half-life of 5.3-8.0 hours. The test compound was rapidly absorbed from the gastrointestinal system and eliminated in the urine (41.5% - 54% during the first 8 hours; 81.9-85.1% of the AD during the first 36 hours). Total urinary excretion of the radioactivity amounted to 82.3-85.8% of the AD by 128 hours after dosing. Excretion of the radioactivity in the feces was minimal and occurred mostly within the first 6 hours after dosing (1.87% - 2.61% of the AD). The balance of the AD was not accounted for. The HPLC analysis of the 0-24 hour composited urine of the two volunteers revealed three metabolites with no parent compound present. These were identified by mass spectrometric (MS) analysis as the hydrolysis products of the parent material: Metabolite A: the diacid of MGK 326 (39.8% of the urinary radioactivity), Metabolite B ; 5-carboxy unesterified (3.9% of the urinary radioactivity) and Metabolite C: 2-carboxy unesterified (40.3% of the urinary radioactivity). Metabolites B and C were converted to Metabolite A by acid hydrolysis. **Acceptable/non-guideline**
Non-guideline	42974602	Dermal Absorption & Mass Balance- Humans June 18, 1992. Formulated Pyridine-4-^{14}C-MGK® Repellent 326 (1.1% w/w) with DEET (17.5% w/w) and MGK 264 (5% w/w). 46.6 ug/cm^2 in isopropanol. 3 healthy human volunteers.	Plasma radioactivity levels indicated that the formulated ^{14}C-MGK® 326 was continuously absorbed through the human skin, and a peak plasma concentration was reached when the exposure was terminated. Plasma radioactivity levels dipped after isopropanol wash. **Mean dermal absorption of radiolabeled MGK-326 (sum of radioactivity in urine and feces) from an 8 hr exposure was 3.4% (cumulative total measured over 128 hrs)**. Absorbed radioactivity was eliminated mainly in the urine and only negligible amounts were eliminated in the feces. The majority of unabsorbed dose was found in the isopropyl alcohol swabs (78%). Mean total recovery of applied dose was 102.17%

Non-guideline	42974601	Dermal Absorption & Mass Balance- Humans June 17, 1992. Pyridine-4-^{14}C- MGK® Repellent 326. 41.7 ug/cm^2 in isopropanol 4 healthy human volunteers	Plasma radioactivity levels indicated that ^{14}C-MGK® 326 was steadily absorbed through the human skin, and a peak plasma concentration was reached when the exposure was terminated at 8 hours. **Mean dermal absorption of radiolabeled MGK-326 (sum of radioactivity in urine and feces) from an 8 hr exposure was 24.9% (cumulative total measured over 128 hrs).** Absorbed radioactivity was eliminated mainly in the urine (24.7% of the applied dose) and only negligible amounts were eliminated in the feces. The majority of unabsorbed dose was found in the isopropanol wash (48.5%). Mean total recovery of applied dose was 95.5%.
Non-guideline	42732101	Dermal Absorption & Mass Balance: Multiple Dosing - Humans February 25, 1993. Formulated Pyridine-4-^{14}C-MGK® Repellent 326 (1.0% w/w) with DEET (17.5% w/w) and MGK 264 (5% w/w). 4.2 ug/cm^2 daily for 14 days followed by 4.2 ug/cm^2 of the labeled material (37.9 uC) on day 15.	Plasma radioactivity levels indicated that the formulated ^{14}C-MGK® 326 was continuously absorbed through the human skin, and peaked when the exposure was terminated. The plasma radioactivity levels as a function of time were analogous to those obtained with single dose dermal application of the pure material (MRID 42974601) and the formulated material (MRID 42974602). **Mean dermal absorption of radiolabeled MGK-326 (sum of radioactivity in urine and feces) from an 8 hr exposure was 4.75% (cumulative total measured over 128 hrs).** Absorbed radioactivity was eliminated mainly in the urine and only negligible amounts were eliminated in the feces. The majority of unabsorbed dose was found in the isopropyl alcohol swabs (79%). Mean total recovery of applied dose was 99.28.
85-3 870.7600	42246503	Dermal Absorption - Rats January 20, 1990. Pyridine-4-^{14}C- MGK® Repellent 326. **Group 1**: Five male rats 80 ug/cm^2 in isopropanol. Blood collected over 168 h. **Groups 2-5**: Five males/group 60 ug/cm^2 , sacrificed at 1, 10 , 19 or 168 hours.	The test material was absorbed through the skin and rapidly reached a peak blood level (13% of the administered dose) at 1 hour after dosing and gradually declining reaching a plateau level after 24 hours. The study author calculated a first half life of 9 hours and a second half life of 19 hours. **Mean dermal absorption of radiolabeled MGK-326 (the sum of radioactivity in urine (major amount), feces, tissues/carcass, and cage wash) after 10 hours of exposure was 45%.** Mean recoveries of the test material ranged from (95-103%). The majority of recovered test material was found in the skin rinse at the 1 and 10 hr time intervals (86 and 53% respectively). Mean amounts of test substance found in the skin rinse decreased significantly at the 19 and 168 hr time intervals (31 and 7% respectively) indicating that material remaining in/on the skin continues to be absorbed over time.

GL #	MRID	Study Type	Results and Classification
Non-guideline	43033301	Hepatic Enzyme Induction Study - Rats, April 9, 1992 99.7% purity 0, 96.9, 373.4, 783.9 or 1554.5 mg/kg/day for 28 days to males. Positive control: Sodium phenobarbital (PhB: 53.7 mg/kg/day	MGK 326 did not affect serum chemistries. It did not produce peroxisomal proliferation, induce peroxisomal enzymes (palmitoyl-CoA oxidation) or induce cytochrome P450 dependent mixed function oxidase enzymes including *N*-ethylmorphine *N*-demethylase, 7-ethoxycoumarin *O*-deethylase, 7-ethoxyresorufin *O*-deethylase or amma-glutamyl-transferase. MGK 326 was not a rat liver microsomal enzyme inducer. **Acceptable/non-guideline**
Non-guideline	42974603	Whole Body Autoradiography Study - Rat. March 16, 1992. 99.7% purity Pyridine-4-^{14}C- MGK® Repellent 326, 100 mg/kg body weight	Only xeroxed copies of the original autoradiograms were submitted in the report and were difficult to evaluate due to their poor quality. No quantitative data on the distribution of the radioactivity in the various tissues and body regions were presented in the report. **Unacceptable/Non-Guideline**. This type of study was not required and HED did not encourage the Registrant to conduct such study.

MGK 326: Acute Toxicity

GL #	MRID	Study Type	Results and Classification
81-1 870.1100	00155068	Acute Oral-Rats, October 31, 1985 Purity? 3160, 3980, 5000, 6310, 7940, or 10000 mg/kg bw	**LD_{50} Males = 5850 mg/kg bw** **Females = 4270 mg/kg bw** **Combined = 5120 mg/kg bw** Toxicity Category III **acceptable/guideline**
81-5 870.2500	41826505	Acute Dermal Irritation - Rabbits, March 12, 1991 purity? MGK® Insect Repellent Spray 2559	**Not a dermal irritant.** Toxicity Category IV
81-2 870.1200	41648601	Acute Dermal - Rabbits, August 30, 190 99% purity Limit dose of 2.0 g/kg	**LD_{50} Males anfd females = >2.0 g/kg** Toxicity Category III **Acceptable/guideline**
81-3 870.1300	41571501	Acute Inhalation-Rats, July 24, 1990 MGK® Repellent 326 Code No. 392-90 One dose 6.09 mg/l (nominal concentration of 39.5, 15.3, and 6.5 mg/ml, respectively).	**LC_{50} : Combined = >6.09 mg/L** toxicity Category IV **acceptable/guideline**
81-4 870.2400	41800501	Primary eye Irritation - Rabbits, Sept. 10, 1990 MGK® Repellent 326 Code No. 392-90	Conjunctival irritation (redness and chemosis) and/or clear discharge were observed for up to 48 hours in the treated eyes. No iritis or corneal opacity was observed. All eyes appeared normal by 72 hours after instillation. not an eye irritant Toxicity Category III **acceptable/guideline**
81-6 870.2600	41648602	Skin Sensitization. - Guinea Pigs, auugst 30, 1990 99%	**Not a skin sensitizer**

MGK 326: Mutagenicity Studies

GL #	MRID	Study Type	Results and Classification
84-2 870-5100	40382101	Bacterial reverse mutation September 12, 1986 100% purity 100-5000 ：g/plate tested up to cytotoxic dose.	No mutagenic effect was noted with or without microsomal activation at concentrations up to the toxic range of 5000 micrograms of MGK 326/plate in the initial tests or in the confirmatory assay. **Acceptable/guideline**
84-2 870-5300	40382102	*In Vitro* mammalian cell gene mutation - CHO cells January 14, 1987. 100% purity 0.0001 - 1.0 ：L/ml ± S-9 activated system	MGK repellent 326 was negative for the induction of structural chromosome aberrations in the duplicate assays in the presence and absence of metabolic activation (MA) up to toxic dose levels (0.2 uL/mL without MA; 0.5 and 1.0 uL/mL with MA) **Acceptable/guideline**
84-2 870-5300	40382104	*In Vitro* mammalian cell gene mutation - L5178Y TK+/- Mouse Lymphoma Mutagenesis Assay, December 15, 1986 100% purity 0.13-1.2 or 0.024-0.32 µL/mL ± S-9, respectively	MGK Repellent 326 was tested up to cytotoxic levels (>0.18 µL/mL, -S9 and >0.24 µL/mL, +S9). Increases in mean mutant frequency of at least 2x background with >10% growth were observed in the absence (0.18 µL/mL, trial 4) and presence (1.0 µL/mL, trial 1; 0.9 and 1.2 µL/mL, trial 2) of S9-activation; however, because the results were not reproducible (-S9) and there was no clear dose-response observed in any trial (+ or -S9), the results of the study are considered equivocal **Acceptable/guideline**
84-2 870-5550	40382103	Unscheduled DNA synthesis in Rat Primary Hepatocytes , April 20, 1987, 100% a.i. 0.001 - 0.2 ：L/mL tested	MGK Repellent 326 was tested up to cytotoxic levels (0.06 µL/mL) as determined by increased levels of lactic acid dehydrogenase (LDH) activity. No significant increases in mean net nuclear grains (NNG) or percent cells in repair were observed compared to controls. The positive control, dimethylbenz(a)anthracene (DMBA), induced the appropriate response. **Acceptable/guideline**.

9.2 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Summary of Toxicology Endpoint Selection for MGK® Repellent 326

Exposure Scenario	Dose (mg/kg/day)	*Special FQPA Safety Factor and Level of Concern for Risk Assessment	Endpoint for Risk Assessment
Dietary Risk Assessments			
Acute Dietary all populations	Not Applicable		
Chronic Dietary all populations	Not Applicable		
Non-Dietary Risk Assessments			
Incidental Oral Short-Term (1 - 30 Days)	NOAEL= 65	**FQPA SF = N/A** **LOC for MOE**** = 100	**2-Gen. Repro. Study** LOAEL = 250 mg/kg/day based on decreased body weight on lactation day 21.
Incidental Oral Intermediate-Term (1 - 6 Months)	NOAEL= 65	**FQPA SF = N/A** **LOC for MOE** = 100	**2-Gen. Repro. Study** LOAEL = 250 mg/kg/day based on decreased body weight on lactation day 21.
Dermal Short-Term (1 - 30 days)	Oral NOAEL= 65	**FQPA SF = N/A** **LOC for MOE** = 100	**2-Gen. Repro. Study** LOAEL = 250 mg/kg/day based on decreased body weight on lactation day 21.
Dermal Intermediate-Term (1 - 6 Months)	Oral NOAEL= 65	**FQPA SF = N/A** **LOC for MOE** = 100	**2-Gen. Repro. Study** LOAEL = 250 mg/kg/day based on decreased body weight on lactation day 21.
Dermal Long-Term (> 6 Months)	Not required use pattern		
Inhalation Short-Term (1 - 30 days)	Inhalation NOAEL= 60	**FQPA SF = N/A** **LOC for MOE** = 100	90 - day Inhalation - Rat LOAEL = 60 mg/kg/day based on lack of toxicity at highest dose tested

Exposure Scenario	Dose (mg/kg/day)	*Special FQPA Safety Factor and Level of Concern for Risk Assessment	Endpoint for Risk Assessment
Inhalation Intermediate-Term (1 - 6 Months)	Inhalation NOAEL= 60	**FQPA SF = N/A** **LOC for MOE** = 100	90 - day Inhalation - Rat LOAEL = 60 mg/kg/day based on lack of toxicity at highest dose tested
Inhalation Long-Term (>6 Months)	Inhalation NOAEL= 60	**FQPA SF = N/A** **LOC for MOE** = 100	90 - day Inhalation - Rat LOAEL = 60 mg/kg/day based on lack of toxicity at highest dose tested
Cancer	**Classification:** B2: probable human carcinogen based on multiple malignant and benign tumors in the rat and in the mouse. **Q1*** = 1.63×10^{-3} $(mg/kg/day)^{-1}$ based on liver adenomas, carcinomas and combined adenomas/carcinomas in male rats.		

Dermal Absorption Factor: 5%

**** NOTE:*** Since MGK Repellent 326 is not registered for use in/on foods and has no published or proposed tolerances, the special FQPA safety factor is **not applicable (N/A)** to risk assessments for this chemical.

** LOC for MOE: Level of Concern for Margin of Safety